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(54) Ester of L-carnitine with gamma-hydroxybutyric acid and pharmaceutical compositions containing it for inhibiting neuronal degeneration and for the treatment of coma.

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EP-A- 0 167 115
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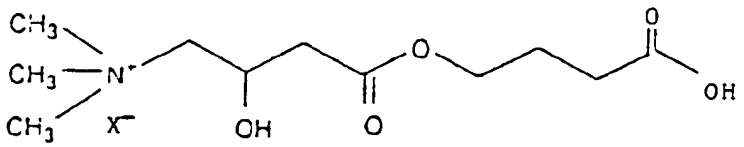
Description

The present invention relates to the L-carnitine ester with gamma-hydroxybutyric acid and its pharmacologically acceptable salts of formula (I)



(I)

wherein X^- is the anion of a pharmacologically acceptable salt, e.g. chloride, bromide, orotate, acid aspartate, acid citrate, acid phosphate, acid fumarate, lactate, acid maleate, acid oxalate, acid sulfate and glucosephosphate.

These compounds are active in inhibiting neuronal degeneration (as it occurs in Alzheimer's senile dementia and Parkinson's disease) and in the treatment of coma.

The present invention also relates to orally or parenterally administrable pharmaceutical compositions for treating the foregoing pathologies, which comprise one of the compounds of formula (I) as active principle.

Whereas, from a theoretical viewpoint, from carnitine and gamma-hydroxybutyric acid three distinct compounds can be obtained, namely:

(i) the salt

(ii) a first ester, by condensation of the acid OH with the carnitine carboxyl group; and

(iii) a second ester, by condensation of the acid carboxyl group with the carnitine OH,

the compound of the present invention is the ester (ii), i.e. the compound wherein the ester bond is formed through the carnitine carboxyl group.

Esters of carnitine with hydroxy-substituted saturated organic acids (e.g. 2-hydroxybutyric, 2-hydroxy-2-methylbutyric and 2-methyl-3-hydroxy propionic acid) are known already; see e.g. US patent 4,766,222 assigned to Sigma-Tau Industrie Farmaceutiche Riunite S.p.A. These compounds, however, are 0-esters (i.e. esters on the carnitine hydroxyl group of type (iii)) and endowed with pharmacological properties entirely different from and in no way related to the properties of the ester of the present invention.

Esters on the carnitine carboxyl group are described in Z. Physiol. Chem., 295, 377, 1953 e Z. Physiol. Chem., 346, 314, 1966. These are, however, esters of carnitine with aliphatic alcohol, such as methanol, ethanol and butanol, or with aromatic alcohols such as benzyl alcohol, not with hydroxy-acids.

The example that follows shows the preparation of the ester of L-carnitine chloride with gamma-hydroxybutyric acid via the synthesis scheme which is illustrated on page 5.

EXAMPLE

Preparation of the ester of L-carnitine chloride with gamma-hydroxybutyric acid (ST 701).

STEP A: Preparation of the benzyl ester of gamma-hydroxybutyric acid.

Gamma-bromobutyric acid (3.3 9; 0.02 moles) was suspended in benzyl alcohol (15 ml). The resulting suspention was cooled to 0°C and thionyl chloride (8 ml; 0.01 moles) was slowly dropwise added thereto. The mixture was kept at room temperature for 16 hours, then concentrated under vacuum in order to remove thionyl chloride and distilled to remove benzyl alcohol. The distillation residue was shown to be the title compound.
TLC Hexane 6 - AcOEt4 R_f=0.8
NMR $COCl_3$ δ ((7.2(5H,s,aromatic); 5.0(2H,s,benzyl CH_2)3.3(2H,t,CH_2COO); 2.6-2.0(4H,m $BrCH_2CH_2$)

STEP B: Preparation of the ester of L-carnitine with gamma-bromo benzylbutyrate.

Carnitine inner salt (0.8 g; 0.005 moles) was suspended in 10 ml anhydrous dimethylformamide. To the suspension gamma-bromobutyric acid benzyl ester (1.3 g; 0.005 moles) was added. The reaction mixture was kept under stirring at 60°C for 48 hours under a nitrogen stream and then distilled under vacuum in order to wholly remove the solvent; 1.3 g of residue were thus obtained which was shown to be the title product.
TLC $CHCl_3$4.2-H_2O 1.1-Isopr OH 0.7 - CH_3COOH 1.1 MetOH 2.8 R_f=0.8
NMR D_2O δ 7.4(5H,s,aromatic); 5.2(2H,s,benzyl CH_2); 4.6(1H,m,CHOH);

4.2(2H,m,O-CH_2);3.6(2H,m,$\overset{+}{N}CH_2$);3.3(9H,s,$(CH_3)_3\overset{+}{N}$;
3.0(2H,d,CH-CH_2COO); 2.6(2H,m,CH_2CH_2COO); 2.0(2H,m,$CH_2CH_2CH_2$)

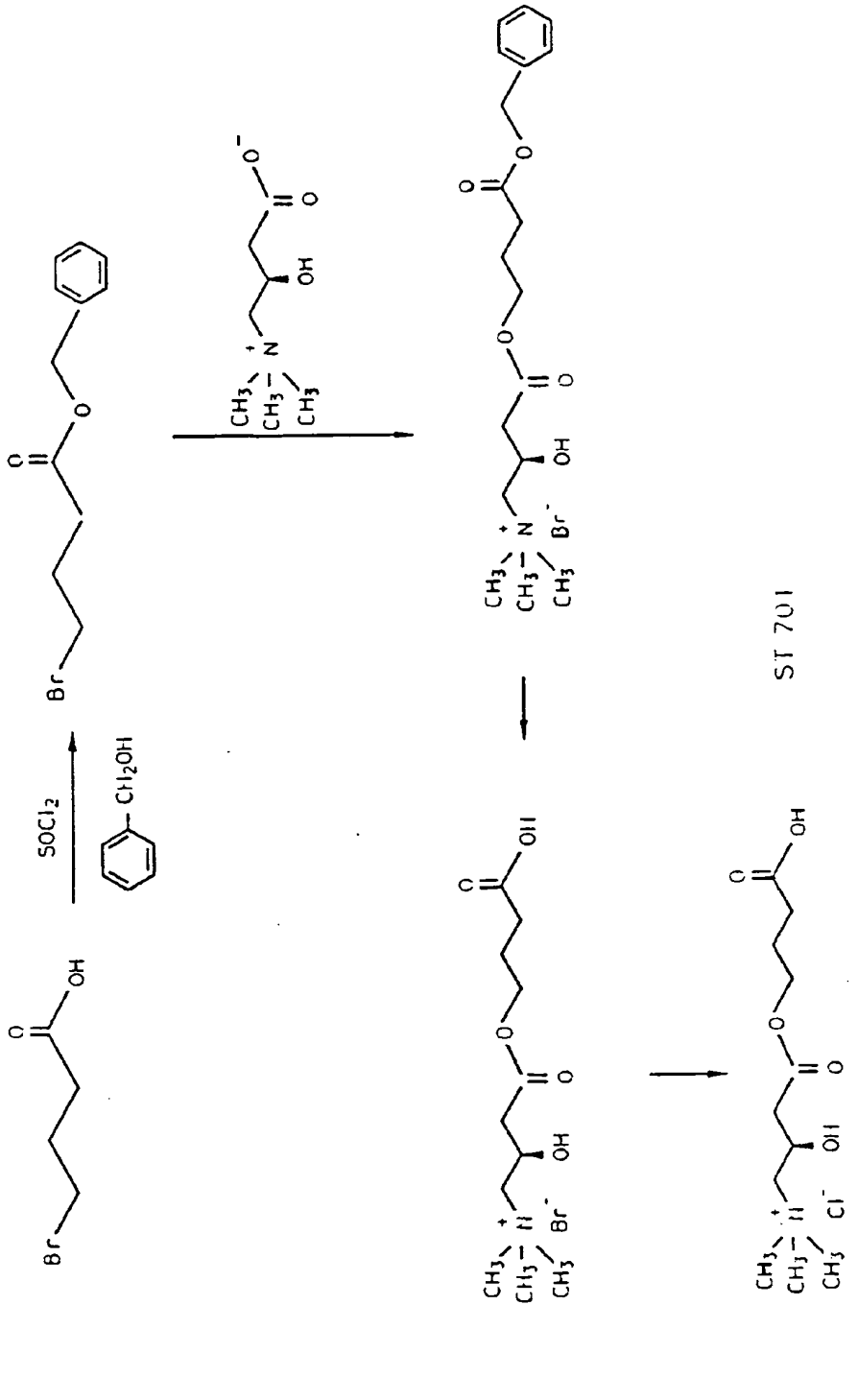
STEP C: Preparation of the ester of L-carnitine bromide with gamma-hydroxybutyric acid.

The product of step B(1.3 g) was dissolved in 20 ml of a H_2O-ethanol (1:1 by volume) mixture. The solution was hydrogenated in the presence of 150 mg 10% Pd/C at 3 atmospheres of hydrogen for 2 hours. The mixture was filtered and concentrated under vacuum. One gram of the title product was obtained.
TLC as in step B R_f=0.6

STEP D: Preparation of the ester of L-carnitine chloride with gamma-hydroxybutyric acid (ST 701).

The product of step C (1 g) was eluted over 30 ml Amberlite IRA 402 strongly basic resin activated to Cl^- form. The eluate was lyophilized. An extremely hygroscopic solid product was obtained.
NMR (D_2O): δ 4.2(2H,t,-CH_2O-); 3.5(2H,d,-N^+CH_2-); 3.2(9H,s,$(CH_3)_3N^+$);
2, (2H,d,CH_2COO); 2.4(2H,m,CH_2COOH); 2.0(2H,m,CH_2-CH_2COOH).
$[\alpha]_D^{25}$=-13.2 (c=1, H_2O)
HPLC
Spherisorb column SCX5M
Eluant: 0.005 M KH_2PO_4 -CH_3CN (35-65); pH=4.2
Flow rate: 1 ml/min.
Detector: UV 205 nm
ST 701 R_T=7.8
Carnitine R_T=10.02 0.5%

Synthesis scheme of L-carnitine chloride with gamma-hydroxybutyric acid (ST 701)



The compounds of the present invention are orally or parenterally administered, in any of the usual phar-

maceutical forms which are prepared by conventional procedures well-kown to those persons skilled in the pharmaceutical technology. These forms include solid and liquid oral unit dosage forms such as tablets, capsules, solutions, syrups and the like as well as injectable forms, such as sterile solutions for ampoules and phials.

For these pharmaceutical forms the usual solvents, diluents and excipients are used. Optionally, sweetening, flavouring and preservative agents can also be present. Non limiting examples of such agents are sodium carboxymethylcellulose, polysorbate, mannitol, sorbitol, starch, avicel, talcum and other agents which will be apparent to those skilled in the pharmaceutical technology.

The dose which is administered will be determined by the attending physician having regard to the age, weight and general conditions of the patient, utilizing sound professional judgement. Although effective results can be noticed at doses as low as 5 to 8 mg/kg of body weight daily, a dose of from about 10 to about 50 mg/kg of body weight is preferred. Whenever necessary, larger doses can be safely administered in view of the low toxicity of the compounds of this invention.

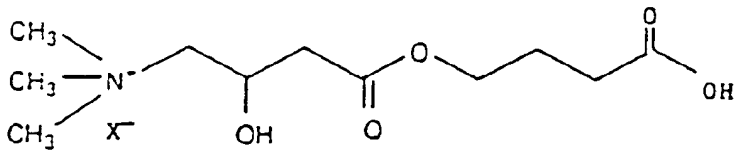
As non-limiting examples and depending on the specific pharmaceutical form of administration, the following dosages can be indicated:

for the phials	: from 5 to 500 mg
for the capsules	: from 15 to 50 mg
for the tablets	: from 15 to 500 mg
for the oral solutions	: from 15 to 50 mg

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, LI, LU, NL, SE

1. The L-carnitine ester with gamma-hydroxybutyric acid and its pharmacologically acceptable salts of formula (I)



(I)

wherein X^- is the an ion of a pharmacologically acceptable salt.

2. Ester according to claim 1, wherein X^- is selected from chloride, bromide orotate, acid aspartate, acid citrate, acid phosphate, acid fumarate, lactate, acid maleate, acid oxalate, acid sulfate and glucosephosphate.

3. An orally or parenterally administrable composition comprising the ester of L-carnitine with gamma-hydroxybutyric acid or a pharmacologically acceptable salt thereof as active principle.

4. An orally or parenterally administrable composition for inhibiting neuronal degeneration and for the treatment of coma comprising the ester of L-carnitine with gamma-hydroxybutyric acid and a pharmacologically acceptable excipient therefor.

5. Composition according to claim 4, in unit dosage form, comprising between about 5 and about 500 mg of L-carnitine ester with gamma-hydroxybutyric acid or an equivalent amount of a pharmacologically acceptable salt thereof.

Claims for the following Contracting States : GR, ES

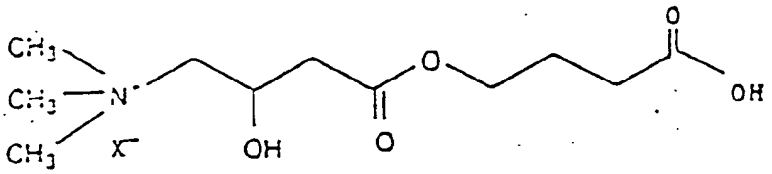
1. A process for producing the ester of L-carnitine with gamma-hydroxybutyric acid, which comprises:
   (a) reacting L-carnitine salt with the benzyl ester of gamma-bromobutyric acid in an anhydrous organic solvent at a temperature comprised between 25°C and 80°C, preferably at 60-70°C, for 12-48 hours in an inert gas atmosphere, obtaining the ester of L-carnitine bromide with gamma-hydroxybutyric acid

benzyl ester;
(b) distilling off the solvent under vacuum until total removal of the solvent is achieved, dissolving the residue thus obtained in water and hydrogenating the solution in the presence of a 5% or 10% Pd/C hydrogenation catalyst under a pressure of 3-5 atmospheres of hydrogen, for 1-5 hours, obtaining the ester of L-carnitine bromide with gamma-hydroxybutyric acid;
(c) filtering the solution of step (b) and eluting it through a strongly basic IRA 402 AMBERLITE ® resin activated either in Cl^- or HCO_3^- form, thus obtaining the desired compound as a chloride or as inner salt, respectively.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, LI, LU, NL, SE

1. L-Carnitin-Ester mit gamma-Hydroxybuttersäure und seine pharmakologisch akzeptablen Salze der Formel (I)



(I)

worin X^- das Anion eines pharmakologisch akzeptablen Salzes ist.

2. Ester nach Anspruch 1, worin X^- ausgewählt ist aus Chlorid, Bromid, Orotat, Säureaspartat, Säurezitrat, Säurephosphat, Säurefumarat, Lactat, Säuremaleat, Säureoxalat, Säuresulfat und Glucosephosphat.

3. Oral oder parenteral verabreichbare Zusammensetzung, umfassend den Ester von L-Carnitin, mit gamma-Hydroxybuttersäure oder ein pharmakologisch akzeptables Salz davon als Hauptbestandteil.

4. Oral oder parenteral verabreichbare Zusammensetzung zum Inhibieren von neuronaler Degenerierung und für die Behandlung von Koma, umfassend den Ester von L-Carnitin mit gamma-Hydroxybuttersäure und einen pharmakologisch akzeptablen Exzipienten dafür.

5. Zusammensetzung nach Anspruch 4, in Einheitsdosierungsform, umfassend zwischen etwa 5 und etwa 500 mg L-Carnitinester mit gamma-Hydroxybuttersäure oder eine äquivalente Menge eines pharmakologisch akzeptablen Salzes davon.

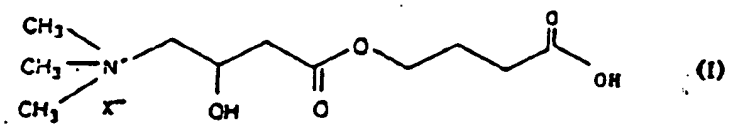
Patentansprüche für folgende Vertragsstaaten : GR, ES

1. Verfahren für die Herstellung des Esters von L-Carnitin mit gamma-Hydroxybuttersäure, umfassend:
(a) Reaktion von L-Canitinsalz mit dem Benzylester von gamma-Brombuttersäure in einem wasserfreien organischen Lösungsmittel bei einer Temperatur zwischen 25 und 80°C, vorzugsweise bei 60 bis 70°C, für 12 bis 48 Stunden in einer Inertgasatmosphäre, Erhalt des Esters von L-Carnitinbromid mit gamma-Hydroxybuttersäurebenzylester;
(b) Abdestillieren des Lösungsmittels unter Vakuum, bis die vollständige Entfernung des Lösungsmittels erzielt wird, Auflösen des somit erhaltenen Restes in Wasser und Hydrieren der Lösung in der Gegenwart eines 5%-igen oder 10%-igen Pd/C-Hydrierungskatalysators, unter einem Druck von 3 bis 5 Atmosphären Wasserstoff für 1 bis 5 Stunden, Erhalt des Esters von L-Carnitinbromid mit gamma-Hydroxybuttersäure;
(c) Filtrieren der Lösung von Schritt (b) und Eluieren dieser durch ein stark basisches IRA 402 AMBERLITE® Harz, aktiviert entweder in Cl^- oder HCO_3^--Form, unter Erhalt der gewünschten Verbindung als ein Chlorid bzw. ein inneres Salz.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, LI, LU, NL, SE

1. Ester de L-carnitine avec l'acide gamma-hydroxybutyrique et ses sels pharmacologiquement acceptables de formule (I)



(I)

dans laquelle X^- est l'anion d'un sel pharmacologiquement acceptable.

2. Ester selon la revendication 1, dans laquelle X^- est choisi parmi un chlorure, un bromure, un orotate, un aspartate acide, un citrate acide, un phosphate acide, un fumarate acide, un lactate acide, un maléate acide, un oxalate acide, un sulfate acide et un phosphate de glucose.

3. Composition administrable par voie orale ou parentérale, comprenant l'ester de L-carnitine avec l'acide gamma-hydroxybutyrique ou un de leurs sels pharmacologiquement acceptables comme principe actif.

4. Composition administrable par voie orale ou parentérale pour inhiber la dégénérescence neuronale et pour le traitement du coma, comprenant l'ester de L-carnitine avec l'acide gamma-hydroxybutyrique et un excipient pharmacologiquement acceptable pour ce dernier.

5. Composition selon la revendication 4, sous forme posologique unitaire, comprenant entre environ 5 et 500 mg d'ester de L-carnitine avec l'acide gamma-hydroxybutyrique ou une quantité équivalente d'un de ses sels pharmacologiguement acceptables.

Revendications pour les Etats contractants suivants : GR, ES

1. Procédé de production de l'ester de L-carnitine avec l'acide gamma-hydroxybutyrique, qui comprend :
   (a) la réaction du sel de L-carnitine avec l'ester benzylique d'acide gamma-bromobutyrique, dans un solvant organique anhydre, à une température comprise entre 25°C et 80°C, de préférence à 60-70°C, pendant 12-48 heures, dans une atmosphère de gaz inerte, pour obtenir l'ester de bromure L-carnitine avec l'ester benzylique d'acide gamma-hydroxybutyrique ;
   (b) l'élimination par distillation du solvant sous vide, jusqu'à élimination totale du solvant, la dissolution du résidu obtenu dans de l'eau et l'hydrogénation de la solution en présence d'un catalyseur d'hydrogénation Pd/C à 5% ou à 10%, sous une pression de 3-5 atmosphères d'hydrogène, pendant 1-5 heures, pour obtenir l'ester de bromure de L-carnitine avec l'acide gamma-hydroxybutyrique ;
   (c) le filtrage de la solution de l'étape (b) et son élution à travers une résine fortement basique AMBERLITE® IRA 402 activée sous forme Cl^- ou HCO_3^-, pour obtenir le composé souhaité sous forme de chlorure ou de sel interne, respectivement.